AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph beginning at page 11, line 11 with the following amended paragraph:

Using HER-2/*neu* as an example, four frozen cell calibrator pellets corresponding to HER-2/*neu* expressing cells, for which the ELISA-determined amount (*f*mol) of HER-2/*neu* per mg protein was known, were cut and stained along with patient's tissue sections in each round of staining. For each tissue, two portions were examined – one embedded in O.C.T. (Optimal Cutting Temperature, Baxter Scientific Products, McGraw Park, IL) for frozen sectioning and another that was ground in liquid nitrogen and placed in homogenization buffer to be used in an ELISA assay. The ELISA portion of each tissue was processed for HER-2/*neu* using the ~~Calbiochem~~CALBIOCHEM® ELISA Kit. These stained slides were then quantitated using image analysis to determine the average O.D. (HER-2/*neu*). The amount of HER-2/*neu* protein expressed in the calibrator cell lines as determined by ELISA and image analysis are shown in Table II.

Please replace the paragraph beginning at page 13, line 8 with the following amended paragraph:

MCF7 (obtained from the Michigan Cancer Foundation, Detroit, MI) and MCF7/HER-2/*neu* cells expressing 5-8 fold elevated expression of HER-2/*neu*, which were generated previously by transduction of MCF7 cells with an ErbB-2 cDNA expression vector (Bacus *et al.*, 1996; Peles *et al.*, 1993; Daly *et al.*, 1997), were grown in RPMI® 1640 (Gibco, Grand Island, NY) supplemented with 10% fetal bovine serum, penicillin (100 μg/ml), in a humidified incubator with 8% CO_2 in air at 37°C. The cells were induced to undergo apoptosis under increasing hypoxic conditions in the presence or absence of the PI3 kinase/Akt inhibitor Wortmannin (~~Calbiochem~~CALBIOCHEM® San Diego, CA). Cells treated with Wortmannin were exposed to 50 μM of the inhibitor 7-48 hours after cell plating and for 1-3 days thereafter. Under hypoxic conditions, the MCF7 cells were sensitive to apoptosis. The presence of

Wortmannin had only a marginal effect on the survival of MCF7 cells under hypoxia. However, the MCF7/HER-2/*neu* cells resisted apoptosis under hypoxia, while the viability of the MCF7/HER-2/*neu* cells exposed to Wortmannin was greatly reduced. Cellular resistance to hypoxia in cells over-expressing HER-2/*neu* is therefore associated with activation of the AKT pathways. The role of PI3 kinase/AKT and HER-2/*neu* pathways in cell survival under hypoxia was confirmed by growing various cell lines in hypoxic conditions and correlating survival with expression of HER-2/*neu*.

Please replace the paragraph beginning at page 13, line 26 with the following amended paragraph:

MDA-MB-435 and MDA-MB-435/HER-2 cells were obtained from Dr. Yu at the UTMD Anderson Cancer Center, Houston, TX. Cells were grown in RPMI® 1640 supplemented as above in 8% CO_2 at 37°C. Western blotting was done as follows. Cells were lysed in lysis buffer (50 mM Tris-HCl, pH 7.4, 150 mM sodium chloride, 1 mM EDTA, 1% Nonidet P-40, 1 mM sodium orthovanadate, 1 mM sodium fluoride, 1 mM phenylmethylsulfonyl fluoride, 2 ug/ml pepstatin, 2 ug/ml leupeptin, 2 ug/ml aprotinin), centrifuged at 4°C for 5 min at 6500g, and protein concentration was determined with a BioRad Protein Assay Kit (BioRad, Hercules, CA). Proteins were separated by electrophoresis using a Bis-Tris NuPAGE system with 1x MOPS running buffer (Novex, San Diego, CA) and transferred to Hybond C-extra membrane (Amersham Pharmacia Biotech, Piscataway, NJ). Membranes were blocked with non-fat dry milk, incubated with the appropriate antibodies, washed with PBS (phosphate buffered saline) and incubated with horseradish peroxidase-conjugated secondary antibody. Detection was carried out with Renaissance Chemiluminescence Reagent Plus (NEN Life Science, Boston, MA). The MDA-MB-435/HER-2 cells over-express HER-2/*neu* 10-fold compared with the parental MDA-MB-435 cell line as determined by Western blot analysis. Lysates from these cells were collected and AKT-2 expression was examined by Western blot analysis with two different antibodies against AKT-2, a polyclonal antibody (Santa Cruz, CA) and a monoclonal antibody (Dr. Testa, Fox Chase Cancer Center, Philadelphia, PA). An increase in the levels of AKT-2 was observed in the cells over-expressing HER-2/*neu*.